UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE BRISTOL-MYERS SQUIBB SECURITIES LITIGATION	:	Civil Action No. 00-1990 (SRC)
	:	Return Date: June 6, 2005

LEAD PLAINTIFF'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION *IN LIMINE* TO EXCLUDE TESTIMONY OF EXPERT WITNESSES DRS. WILLIAM WHITE, ELIZABETH OFILI, ELIJAH SAUNDERS, MATTHEW WEIR AND STEPHEN KIMMEL ON DAUBERT GROUNDS AND TO STRIKE THIS TESTIMONY FROM DEFENDANTS' SUMMARY JUDGMENT RECORD

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PRELIMINARY STATEMENT

Lead Plaintiff, the LongView Collective Investment Fund ("Lead Plaintiff"), respectfully submits this memorandum of law in support of its motion *in limine*, pursuant to Fed. R. Evid. 104 and 702 through 704, to exclude certain testimony of defendants' four "Cardiovascular/ Hypertension/Clinical Trials" experts, Drs. William White, Elizabeth Ofili, Elijah Saunders and Matthew Weir, together with that of their epidemiology expert, Dr. Stephen Kimmel, and to strike that testimony from defendants' summary judgment record. Defendant Bristol-Myers Squibb ("BMS" or the "Company"), along with individual defendants Charles A. Heimbold ("Heimbold"), Peter R. Dolan ("Dolan") and Peter S. Ringrose ("Ringrose") (collectively, "Defendants"), have proffered expert evidence from 18 witnesses in support of their joint motion for summary judgment and defenses in this action.[1]

STATEMENT OF FACTS

In light of the recent submission of papers in support and opposition to Defendants' motion for summary judgment and the Court's August 30, 2004 opinion, familiarity with the facts underlying the claims is presumed. Drs. White, Ofili, Saunders and Weir are all physicians who have been designated by Defendants to opine on cardiology, hypertension and the clinical trial process. They have each submitted expert reports that opine on essentially the same areas: (1) hypertension and heart failure; (2) Vanlev's "risk/benefit profile"; and clinical trials generally

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[1] Defendants' expert reports were submitted as exhibits 11-28 to the Declaration of Samira Shah, Esq. in Support of Defendants' Motion for Summary Judgment, dated December 17, 2004. To the extent any exhibits cited herein were submitted in support or opposition to Defendants' summary judgment motion, they will be referred to as either "PX" or "DX" and will bear their original summary judgment reference number. Any new exhibits, which were not submitted either in support or opposition to Defendants' summary judgment motion, are being submitted herewith as exhibits to the Declaration of James W. Johnson, Esq. In Support of Lead Plaintiff's Motions *In Limine* to Exclude Testimony of Defendants' Expert Witnesses on Daubert Grounds and to Strike Such Testimony From Defendants' Summary Judgment Motion, dated May 13, 2005 ("Johnson Decl."), and are referred to as "Pl. Ex. ___."

and with respect to Vanlev's development. In addition to some of this testimony being inadmissible, as discussed herein, there is considerable overlap between the reports that is cumulative and repetitive.

ARGUMENT

I. Legal Standards Governing Admission of Expert Testimony

Rules 702 through 704 of the Federal Rules of Evidence govern the admissibility of expert testimony, subject to the relevancy provisions of Rules 401 through 403. Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. The rule was amended in 2000 in response to Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), and to the many cases applying Daubert, including Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999) and General Elec. Co. v. Joiner, 522 U.S. 136, 140 (1997). More recently, in Schneider v. Fried, 320 F.3d 396, 405 (3d Cir. 2003), the Third Circuit described these requirements as the "trilogy of restrictions on expert testimony: qualification, reliability and fit."

As is well known, in Daubert the Supreme Court directed district courts to perform a screening or "gatekeeping" function to insure that evidence presented by expert witnesses is relevant, reliable, and helpful to the jury's evaluation of such evidence. Daubert, 509 U.S. at 589, 597. In Kumho Tire, the Supreme Court reiterated this role and clarified that the gatekeeper

function applies to all expert testimony, not only scientific testimony. Kumho Tire, 526 U.S. at 151.

In addition to reliability, Rule 702 and Daubert requires that the expert's testimony must "fit" with the facts of the case and assist the trier of fact in its determination of the claims and defenses. As the Third Circuit stated in United States v. Downing, 753 F.2d 1224, 1237 (3d Cir. 1985), admissibility depends, in part, on "the proffered connection between the scientific research or test result to be presented and particular disputed factual issues in the case." Thus, if an opinion is not relevant to the facts of the case, it is not admissible.

Also, proffered opinions must flow from a sound application of methods to the facts of a casein order to be helpful. Although proponents of expert evidence do not have to "prove their case twice," they "have to demonstrate by a preponderance of evidence that their opinions are reliable." In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744 (3d Cir. 1994). Expert opinion based on facts that are indisputably incorrect is also inadmissible, as it is both irrelevant and not helpful to the trier of fact. See, e.g., Guillory v. Bomtar Indus. Inc., 95 F.3d 1320, 1331-1332 (5th Cir. 1996) (excluding testimony based on altered forklift).

Lay person testimony "masquerading" as expert testimony is inadmissible. "[T]here is no more certain test for determining when experts may be used than the common sense inquiry whether the untrained layman would be qualified to determine intelligently and to the best possible degree the particular issue without enlightenment from those having a specialized understanding of the subject in dispute." Fed. R. Evid. 702 advisory committee's note (1972).

Furthermore, although an expert may opine on an ultimate issue of fact, Fed. R. Evid. 704, he "may not substitute his judgment for the jury's. 'When this occurs, the expert acts outside of his limited role of providing the groundwork in the form of an opinion to enable the

jury to make its own informed determination." Crowley, 322 F. Supp. 2d 530, 554 (D.N.J. 2004) (precluding opinion on the credibility or consistency of other testimony and that which summarized facts)(internal citation omitted).

> Under Rules 701 and 702, opinions must be helpful to the trier of fact, and Rule 403 provides for the exclusion of evidence which wastes time. These provisions afford ample assurances against the admission of opinions which would merely tell the jury what result to reach….They also stand ready to exclude opinions phrased in terms of inadequately explored legal criteria.

Fed. R. Evid. 704 advisory committee's note; see also 29 C. Wright & V. Gold, Federal Prac. and Pro. § 6284, p. 379-80 (1997) (same).

In Schieber v. City of Philadelphia, No. 98-5648, 2000 WL 1843246, at *8-*9 (E.D. Pa. Dec. 13, 2000) (civil rights action), the court precluded the plaintiff's proffered police practices expert from testifying that the City's failure to train its police officers caused a violation of the crime victim's constitutional rights, because the opinion amounted to a legal conclusion. Similarly, an expert cannot opine on whether a person acted with a requisite state of mind. See, e.g., United States v. Watson, 260 F.3d 301 (3d Cir. 2001) (rule violated where examination elicited testimony about mental state of defendant or when expert directly refers to intent or mental state); see also Roberson v. City of Philadelphia, No. 99-3574, 2001 WL 210294, at *7 (E.D. Pa. Mar. 1, 2001) (expert could not opine on whether a third-party or their friends feared arrest).

II. Threshold Question of Qualification

Central to the question of admissibility, an expert witness must be qualified to testify to the opinions he intends to express. Fed. R. Evid. 702; Kumho Tire, 526 U.S. 137, 156. In Elcock v. Kmart Corp., 233 F.3d 734 (3d Cir. 2000), the Third Circuit reaffirmed the standard for qualifying an expert:

> Rule 702 requires the witness to have 'specialized knowledge' regarding the area of testimony. The basis of this specialized knowledge 'can be practical experience as well as academic training and credentials.' We have interpreted the specialized knowledge requirement liberally, and have stated that this policy of liberal admissibility of expert testimony 'extends to the substantive as well as the formal qualification of experts.'

Id. at 741 (internal citations omitted). An expert may be excluded when his training and experience is lacking in the particular area in which his testimony is offered. For example in Estate of Lam v. Upjohn Co., No. 94-0033-H, 1995 WL 478844, at *2 (W.D. Va. Apr. 21, 1995) the court excluded expert testimony on pharmaceutical warnings when the expert had "no academic training or regulatory experience and ha[d] never participated in any FDA-related proceedings addressing what constitutes an adequate warning." Thus, "a party cannot qualify an expert generally by showing that the expert has specialized knowledge or training which would qualify him or her to opine on some other issue." In re Diet Drugs Prod. Liab. Litig., No. MDL 1203, 2000 WL 962545, at *3 (E.D. Pa. June 28, 2000).

A. Dr. Weir Is Not Qualified To Give Certain Opinions On Angioedema

In his report (DX 26 ¶¶ 29-31), Dr. Weir not only provides his opinion as to what angioedema is and how to treat it, he further discusses incidents of angioedema referred to in a medical article (a "1993 article in Laryngoscope") and in the FDA's Adverse Event Reporting System. However, Dr. Weir is a nephrologist, not an epidemiologist.

The information he cites is neither within the scope of his expertise, nor is it balanced by, for instance, any attempt to identify the size of the patient populations in which the identified angioedema incidents arose. See also PX 38 134:15-137:4 (admitting that it is impossible to draw conclusions based on the Laryngoscope case reports as to the incidence rate of the reported events). As such, Dr. Weir should be precluded from discussing these materials. Indeed, in his own practice spanning more than 20 years, Dr. Weir has had exactly one patient who presented

with ACE inhibitor-induced angioedema symptoms that he would classify as "severe." (PX 38 13:11-14:18.)

B. Challenges to Dr. Kimmel's Qualifications

Defendants' epidemiology expert, Dr. Stephen Kimmel, is an associate professor of medicine and epidemiology, with a focus on pharmacoepidemiology. (DX 18 ¶ 1.) Five to six percent of his time is spent practicing medicine as a cardiologist (Pl. Ex. 5 9:4-10:4.) Dr. Kimmel opines on "epidemiology-related issues raised by plaintiff's experts" and BMS's "review of and representations about available data regarding angioedema with Vanlev." (DX 18 ¶ 5.) Although Dr. Kimmel is qualified to opine on epidemiology matters, his opinion goes beyond that and into areas of drug development to which he is not qualified to testify.

Although he states in his report that he spends the majority of his time "conducting clinical epidemiology research" (DX 18 ¶ 2), he explained at his deposition that he has not done work on investigational new drugs that is directly related to the study of the drug or "to answer a particular question about the drug." (Pl. Ex. 5 53:14-54:8.) His research relating to new drugs focuses on studies of the target populations for those drugs. Id. The remainder of his research involves post-marketing studies once drugs are approved. (Pl. Ex. 5 54:19-22.)

All his research for pharmaceutical companies has been investigator-initiated in that he creates a proposal or protocol and approaches a company to solicit funding. (Pl. Ex. 5 47:10-48:5.) He has never been employed by a pharmaceutical company or FDA and testified that he does not have direct experience with drug development and the problems that arise during development. (DX 18, Ex. A; Pl. Ex. 5 87:10-89:25.) He does not have any experience identifying safety signals in a new drug development program. (Pl. Ex. 5 111:6-11.) He has not had any experience in setting up monitoring plans for clinically significant adverse drug events in clinical development programs for new drugs. (Pl. Ex. 5 167: 19-168:11.) He has evaluated

safety signals in marketed drugs only once they have been identified by FDA or others. (Pl. Ex. 5 113:3-24.) He distinguished this work from "commercial questions, regulatory issues relating to new drugs." (Pl. Ex. 5 112:20-22.)

When asked whether he has an understanding of how pharmaceutical companies analyze evolving data to make decisions about not bringing a drug to market because of safety problems, Dr. Kimmel answered:

> Again, you said from the drug company's standpoint, from the pharmaceutical industry. I don't know -- I haven't done these kind of premarketing studies, I haven't been involved in drug companies, so I don't know how they do it. I don't know under which circumstances a company may make one decision versus another and one company would make one decision versus another company. I don't have personal knowledge of what goes into that decision-making process.

(Pl. Ex. 5 193:17-194:3.)

In light of this testimony, Dr. Kimmel is not qualified to testify about the reasonableness of Defendants' actions with respect to the development of Vanlev, such as: BMS's "representations about available data regarding angioedema with Vanlev" (DX 18 ¶ 8); whether the occurrence of angioedema "was neither unexpected nor reason in and of itself for alarm" (DX 18 ¶ 16); whether the occurrence of angioedema in the early initial trials was meaningful (DX 18 ¶ 23); whether the pre-OCTAVE angioedema events constituted a safety signal (DC 18 ¶¶ 63, 77); whether "head and neck edema were reasonably estimated separately from angioedema" (DX 18 ¶ 67); and determining whether the risk of angioedema was "unacceptable" with Vanlev (DX 18 ¶ 82).

III. Unreliable Testimony Should Be Excluded

The essential guidance learned from Daubert, Kumho Tire and Joiner is that an expert's testimony must be based upon sufficient facts and flow from the reliable application of sound

reasoning or methods. Fed. R. Evid. 702. "An expert's opinion is reliable if it is 'based on the "methods and procedures of science" rather than on "subjective belief or unsupported speculation"; the expert must have "good grounds" for his or her belief.'" Elcock, 233 F.3d at 745.

The non-exclusive checklist of factors set forth by Daubert and its progeny for courts to use in assessing whether a particular scientific methodology is reliable, and thereby admissible, include: (a) whether a "theory or technique…can be (and has been) tested"; (b) whether it "has been subjected to peer review and publication"; (c) whether, in respect to a particular technique, there is a high "known potential rate of error" and whether there are "standards" controlling the application of the technique; and (d) whether the theory or technique enjoys "general acceptance" within" a "relevant scientific community." Kumho Tire, 526 U.S. 137 at 149 (citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 592-94 (1993)). "The trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable. That is to say, a trial court should consider the specific factors identified in Daubert where they are reasonable measures of the reliability of expert testimony." Id. at 151-152; see also Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 594-95 (D.N.J. 2002) (noting additional factors such as whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion or whether the expert has adequately accounted for alternative explanations), aff'd, No. 02-2331, 2003 WL 21467223 (3d Cir. 2003).

Although an overused phrase, it is applicable to the testimony challenged here: "[N]othing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the *ipse dixit* of the expert. A court

may conclude that there is simply too great an analytical gap between the data and the opinion proffered." Joiner, 522 U.S. at 146.

A. Certain of Dr. White's Opinions Are Unreliable Because They Are Not Based on Sufficient Facts

1. Dr. White Cannot Opine That the Incidence of Angioedema in the Early Vanlev Clinical Trials was Within the Range Reported with Other ACE Inhibitors

Dr. White opined that of the 4284 patients exposed to Vanlev during the early hypertension clinical trials, 0.9% developed angioedema. He then opined that this incidence was within the reported incidence of angioedema with other ACE Inhibitors, which he said was between 0.1 and 1.0%. (DX 27 ¶ 55.) Dr. White cannot identify the basis for this opinion.

In his expert report, Dr. White cited the report prepared in 1999 by BMS employee Joanna Whyte, reviewing the literature on ACE Inhibitors and angioedema as reference for his opinion. (DX 27 ¶ 55.) But in his deposition he testified that he did not look at the Whyte Report in formulating his opinion, although he believed he did look at it at one point in time. (Pl. Ex. 13 98: 15-24.)

He testified that the basis for his opinion, that the incidence of angioedema in large studies of ACE inhibitors was between 0.1 and 1%, was a review of some studies and clinical databases for ACE inhibitors that he has worked on. (Pl. Ex. 13 96:4-25.) Dr. White could not identify the basis with more specificity. Although he referred to clinical trials he had worked on, he also testified that in none of them was the incidence of angioedema as high as one percent. (Pl. Ex. 13 95:6 – 96:3.)

> Q. Where have you seen one percent?
>
> A. Well, whether or not I saw it from clinical trial reports or databases or articles I don't really recollect at this moment, but it is from a global assessment when I was writing the report of reviewing the literature.

> Q. So is it your testimony as you sit here today that you don't remember where specifically you got the number one percent as the upper end of the range of angioedema with ACE inhibitors? Is that right?
>
> A. No, I stated that I actually reviewed the literature, reviewed the studies, and when I was writing the report had felt that there was a range from 0.1% to one percent based on that review.
>
> Q. Okay, and as you sit here today can you tell me anything in particular that you looked at that led you to think that the range of angioedema with ACE inhibitors, the upper end of the range is one percent?
>
> A. I don't recollect the exact citation.

(Pl. Ex. 13 96:4-25.) Dr. White does not know the basis for his opinion that the incidence of angioedema in large trials of ACE inhibitors was 0.1 to 1.0%. His opinion that the incidence of angioedema with Vanlev was within the range experienced with other ACE inhibitors is suspect, unreliable, and unverifiable and must be excluded.

2. <u>Dr. White Cannot Opine That Vanlev Would Achieve Cost Savings</u>

Dr. White opined that many patients who take more than one medication for blood pressure control would be able to substitute Vanlev for two or more other drugs to achieve the same effect at a potential cost savings. (DX 27 ¶ 28.) Dr. White admitted he did not know what Vanlev would cost if it were approved, so he has no basis for his speculation that it could save users money. (Pl. Ex. 13 216:21-217:2.) His opinion must be excluded.

B. Certain of Dr. Ofili's Opinions Are Based On Insufficient Data and Are Inadmissible

1. Dr. Ofili Cannot Opine That Defendants' Failure to Furnish A Definition of Angioedema During the Initial Clinical Trials Avoided Investigator Bias

Dr. Ofili opines that Defendants' failure to give investigators a definition of angioedema was proper clinical trial design, because it avoided investigator bias. (DX 21 ¶ 68.) Her opinion must be excluded because she could not identify a verifiable basis for her opinion.

> Q. Can you refer me to any literature that supports a proposition that providing a definition of an adverse event in a clinical trial introduces investigator bias into the reporting?
>
> A. I cannot point you to a specific literature right now, but I can recommend to you the review, in this particular case, of the various descriptions of angioedema, and how that description has evolved over time. And in the various clinical trials that have been done with ACE inhibitors, how those trial designs have treated angioedema. The double-blind, randomized, efficacy trials.

(DX 21 89:21-90:10.)

She cannot point to any literature, and the rest of her answer does not provide a basis for her opinion that providing a definition of an adverse event introduces bias. Her opinion is unverifiable and must be excluded.

2. Dr. Ofili Cannot Opine that the IRB for the Initial Clinical Trials Could Have Halted the Trial

Dr. Ofili opined that if the local Institutional Review Boards ("IRBs") at any of the multicenter sites of the Vanlev clinical trials had perceived a safety problem they would have halted the trial, thus, there was no need for a DSMB to evaluate interim data to protect patient safety during the initial clinical trials. (DX 21 ¶¶ 74-75). She testified, however, that she was not aware of any study being stopped by an IRB because of safety concerns. She is aware of an instance, or more than one instance, where a local IRB suspended a study because data was not

reported in a timely fashion. However, the study was not terminated; it was suspended to allow the investigators to be more compliant with reporting data. She came across this information in a report. She does not know where she saw the report. It may have been on the internet sometime in the past two or three years. (Pl. Ex. 9 53:8-57:4.) Dr. Ofili could not describe any verifiable basis for her opinion that the local IRBs could have stopped the Vanlev trials for safety reasons. Her opinion must be excluded.

C. Conclusions Dr. Saunders Draws From Limited OCTAVE Data Are Without Foundation and Are Inadmissible

Citing DX 300, Dr. Saunders notes in his report that "those patients who receive enalapril were more likely to suffer from cardiovascular difficulties (such as death or hospitalization for cardiovascular causes) than those patients receiving omapatrilat." (DX 23 ¶18.) This observation, however, is not scientifically or statistically meaningful, and thus should not bear the imprimatur of expert testimony. Any reference to the numerical differences between the Vanlev and enalapril arms of the study concerning "cardiovascular difficulties" must be precluded because the OCTAVE trial was not designed to detect such differences. Indeed, Dr. Saunders himself acknowledged that such differences are not significant at his deposition:

> Q. And any differences that occurred with respect to the number of strokes, heart attacks, deaths in connection with the OCTAVE trial, you wouldn't ascribe any significance to any numerical differences that occurred between the arms of the study, would you?
>
> A. Generally, no. The study wasn't designed for that purpose. But all investigators know that you have to look at it, of course. But the study was not designed for that.

(Pl. Ex. 11 282:9-19, 282:20-283:7.) (Dr. Saunders acknowledging that the numerical differences "could be chance.").

D. Certain of Dr. Kimmel's Opinions Are Unreliable, Because They Are Not Based on Sufficient Facts

Defendants' epidemiology expert, Dr. Kimmel, uses impermissible hearsay to bolster his opinion that the incidence of angioedema with Vanlev was consistent with what was known about ACE inhibitors. (DX 18 ¶¶ 66, 92.) "To be sure, an expert may not be used simply as a vehicle for the admission into evidence of otherwise inadmissible hearsay testimony." Crowley v. Chait, 322 F. Supp. 2d 530 (D.N.J. 2004); see also 29 C. Wright & V. Gold, Fed. Prac. & Pro. § 6273, at 312 (1997) ("Rule 703 does not authorize admitting hearsay on the pretense that it is the basis for expert opinion when, in fact, the expert adds nothing to the out-of-court statements other than transmitting them to the jury.")

Dr. Kimmel states in his report, "My opinions are shared by Dr. Wayne Ray, a Professor of Pharmacoepidemiology at Vanderbilt University who prepared a review of Vanlev and angioedema for BMS in early 2000" and he goes on to describe this agreement. (DX 18 ¶¶ 66, 92.) However, Dr. Kimmel does not explain that Dr. Ray's review is a "draft report" entitled, "Omapatrilat and Angioneurotic Edema, Brief Review and Comparison with other Angiotensin-Converting Enzyme Inhibitors." (Pl. Ex. 33.) Interestingly, the preliminary report notes several things that Dr. Kimmel does not mention. First, Dr. Ray notes:

> *There are two bases for concern that this rate may be higher than that of the pure ACEI.* First, the occurrence of angioedema in the omapatrilat premarketing clinical trials is greater than that for clinical trials for some, but not all, of the pure ACEI. Second, omapatrilat may have a greater effect than the pure ACEI on bradykinin, a leading contender for the mechanism by which ACEI cause angioedema.

(Pl. Ex. 33 at OMAP0091679.0002.) (emphasis added). Dr. Ray states that the objective of his "brief report" is to answer, "Is there any evidence that the frequency of angioedema among users

of omapatrilat is greater than that for users of the pure ACEI." Id. In his conclusion, Dr. Ray wrote:

> 2. However, the development program data *do provide a limited basis for concern. Overall, the occurrence of angioedema in the omapatrilat trials is towards the high end* of the range for other ACEIs, although this could be explained by the factors described in 3.2 above. Also, the development trials that compared omapatrilat to lisinopril *had an excess* of angioedema in the omapatrilat group. Although this internal comparison is based on small numbers, *it does provide a basis for concern*.
>
> * * *
>
> 4. The epidemiologic data on the true incidence of angioedema in ACEI is very imprecise. . . .[t]hus, although the available data are not sufficient to establish a difference between omapatrilat and other ACEI, these data also are *consistent with a substantial difference*. . . .
>
> 5. *If it is clinically important to quantify the difference* in the occurrence of angioedema among patients receiving omapatrilat versus those receiving the pure-ACEI, *then a head-to-head comparison would need to be done* . . . .

(Pl. Ex. 33 at OMAP0091679.0008) (emphasis added).

Dr. Kimmel should not be permitted to testify about what Dr. Ray said or did with respect to Vanlev, because he has no personal knowledge of those matters. Dr. Ray's report is not of a "type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subjects" under Fed. R. Evid. 703.

E. Certain Opinions of Dr. Weir's Are Without Foundation and Are Therefore Inadmissible

1. No Foundation Or Data Underlying Dr. Weir's Opinion Of the Number of Hypertensive Patients Who Will Need More Than One Medication to Achieve Blood Pressure Control

In his report, Dr. Weir states as follows: "Indeed, more than 80% of all patients will require two to five medications to control their blood pressure." (DX 26 ¶ 22.) This opinion, however, is not based on anything resembling a reliable, statistically sound scientific sampling of the nation's hypertensive patient population. Rather, Dr. Weir's opinion is based on his own limited personal and anecdotal experiences, i.e., his medical practice and speaking with other doctors. (PX 38 67:16-23.) It should be precluded and struck from the summary judgment record.

2. Dr. Weir's Opinion About NEP Inhibition Is Without Foundation and Inadmissible

Dr. Weir also states that Vanlev "may provide to the failing heart additional benefits of NEP inhibition that have not yet been recognized." (DX 26 ¶ 37.) He cites no data in support of this proposition and it is nothing more than rank speculation. Indeed, at his deposition Dr. Weir admitted that it is possible that Vanlev may have as yet undiscovered disadvantages also. (PX 38 142:17-143:8.) Dr. Weir's musings about untested and unproven benefits are not based on reliable facts and they do not arise from anything resembling a reliable methodology. Testimony as to possible undiscovered benefits must be precluded.

3. Dr. Weir's Opinions About BMS's Ability to Provide Investigators With a Definition of Angioedema Are Without Foundation and Inadmissible

Dr. Weir also states as follows: "I do not believe that it would have been possible for BMS to provide investigators a workable definition of angioedema during the early clinical

trials." (DX 26 ¶ 49.) As his own deposition testimony demonstrates, however, this opinion if flawed and thus should be precluded:

> Q. You have stated in your report that "I do not believe that it would have been possible for BMS to provide investigators a workable definition of angioedema during the early clinical trial," and I'm on page 21 in paragraph 49, if you want to look at the language.
>
> A. I did state that.
>
> Q. Are you aware that a workable definition of angioedema was provided to investigators in the Octave trial?
>
> A. I'm sure it was.
>
> Q. Do you have any knowledge of what changed between the early clinical trials and the Octave trial that enabled BMS to give investigators a definition in the Octave trial that they were somehow unable to give in the earlier clinical trials?
>
> A. I believe, if memory serves me correct, that -- well, first, angioedema is not easily defined. I have looked in different dictionaries. I've looked in medical texts. I see different ways of describing it, so the fact that there are different ways of describing it, the fact that we know that there are many different causes for it, I think that in the Octave study there was a particular interest in more capably defining it, which had never been done before, and so that was one of the unique aspects of this particular clinical trial.
>
> Q. And, just so I understand your answer, if there had been a particular interest in more capably defining angioedema in, let's say, January of 1998, is there any reason you're aware of that the company could not have done that?
>
> A. I don't know why they would want to do that.
>
> Q. Okay, but that wasn't my question; my question was, is there any reason you're aware of that the company could not have done that?
>
> A. I'm sure they could have done it.

(PX 38 100:2-101:17.) See also PX 38 102:7-103:16 (Dr. Weir testifies that he is unaware of something that would have interfered with BMS defining and studying angioedema and its related consequences as early as January 1997).

4. Dr. Weir's Opinion Regarding Overall Conduct of OCTAVE Is Baseless and Should Be Precluded

Dr. Weir states as follows: "I participated in OCTAVE, and, in my opinion, the study was extremely carefully designed and carried out." (DX 26 ¶ 54.) But all Dr. Weir can recall is "processing the paperwork" to participate in OCTAVE. He does not recall enrolling any patients; he also incorrectly recalled that there was an 8-week abbreviated study report. (PX 38 28:9-15, 123:17-128:3.) Dr. Weir therefore cannot opine on how the study was carried out; this is the domain of an actual fact witness, not an expert.

F. Dr. White Cannot Opine that the FDA Should Have Approved VANLEV for a Wider Population Based on Only Some Selected Data

After considering the full NDA submitted by BMS, all of the clinical trial data, and conducting an eight hour public hearing with an advisory committee on whether to approve VANLEV, the FDA issued an approvable letter saying that if sufficient additional testing were satisfactorily done, with appropriate results, VANLEV could be approved for a narrow segment of the hypertension population resistant to other treatments. (DX 274.) Dr. White testified that he had mixed feelings about the advisory committee's vote against Vanlev, and that he thought the FDA should have approved it for a wider population. (Pl. Ex. 13 120:12-122:22.) Dr. White was not present at the hearing where the FDA Cardiovascular and Renal Drug Advisory Committee Meeting considered BMS' application for approval of Vanlev. Although he did review a transcript of the advisory committee meeting, Dr. White did not review at least two critical FDA reviews by Drs. Stockbridge and Pelayo reviewing the NDA submissions. (PX 84;

PX 376.) Without having reviewed the relevant information considered by the FDA, Dr. White is not qualified to opine on whether the Panel or FDA should have voted to approve the drug.

G. Certain of Dr. Saunders' Opinions Should Be Precluded As They Are Based on Limited and Selected Information

1. Dr. Saunders' Opinion on Vanlev's Favorable Risk/Benefit Profile Is Based on Limited and Selected Information

Dr. Saunders opined that "omapatrilat had and has a favorable risk/benefit profile" and that "[i]n light of this profile" he would recommend its approval as an antihypertensive medication, particularly in difficult-to-treat African-American patients, and would cast a vote in favor of its approval if he were on the FDA's Cardio-Renal Advisory Committee. (DX 23 ¶ 9.) See also DX 23 ¶ 11 ("In my judgment, the benefits of omapatrilat outweighed its risks for the treatment of hypertension and heart failure, and I would have recommended its approval by the FDA."). However, Dr. Saunders' opinion is unreliable as it is based on a one-sided view derived from the selection of documents provided to him by Defendants. For instance, Dr. Saunders was not privy to any of the FDA reviews, of both the initial NDA and OCTAVE NDA, that were critical of Vanlev. (DX 23, Ex. 2; PX 53; 84; 85.) Nor did he read Dr. Pelayo's safety reviews or Dr. Brinker's epidemiologic analyses. (PX 376; DX 73.)

Dr. Saunders was shown a number of these documents at his deposition. With respect to PX 53, which was marked as plaintiff's exhibit 34 at the deposition, Dr. Saunders testified as follows:

> Q. Do you think it would have helped you to have an understanding of what the FDA's view is, or was, of the side effects profile of omapatrilat based on the initial pre-OCTAVE clinical trials?
>
> A. I think that information is useful. Whether or not it would have changed my position based upon my experience as an investigator, I don't know. But I think knowledge is always useful, and they have a lot of experts looking at things, so yes, I would

> certainly look at their information. Whether it would change my position, I don't know.
>
> Q. So as you sit here today, you don't know whether or not viewing the FDA's internal documents on the risk/benefit profile of omapatrilat would have changed your view; is that fair?
>
> A. Correct.

(Pl. Ex. 11 108:10-109:4.)

Likewise, when shown Dr. Brinker's epidemiological analysis of the Vanlev data (DX 73), which was marked as plaintiff's exhibit 35 at the deposition, Dr. Saunders agreed that an epidemiological analysis of omapatrilat relative to other ACE inhibitors would have "definitely" aided him in forming his opinions as to the risk/benefit profile of omapatrilat. (Pl. Ex. 11 180:21-25.) Like PX 53, DX 73 was never shared with Dr. Saunders before Lead Plaintiff's counsel showed him the document at his deposition.

Dr. Saunders candidly admitted that the Brinker analyses may have altered his expert opinion:

> Q. Do you think that you've had an adequate opportunity to review what's in Plaintiff's Exhibit 35 to make an informed decision on the way in which this information affects your opinion on the risk/benefit analysis of omapatrilat?
>
> A. That's a tough question, because I suppose you're asking had this information been available at the time -- I mean I gave you my opinion in terms that I think omapatrilat has a favorable risk/benefit ratio, or benefit/risk ratio, such that I would recommend approval by the FDA. So I think the question now is with this information, would that still be my impression? Is that what you're asking?
>
> Q. Well, it wasn't, but I'll adopt your question, so why don't you answer that question?
>
> A. And the answer is I don't know. I would have to think about it. But I do think that type of a reasoning is a part of – of making the recommendation for a drug.

(Pl. Ex. 11 191:17-192:14.) See also id. at 200:18-201:17 (Dr. Saunders admitted that it "probably would have been of interest" for him to look at the medical safety review report generated by the FDA's Dr. Pelayo (PX 376), marked as plaintiff's deposition exhibit 1524 in forming his opinions with respect to the risk/benefit ratio of Vanlev).

Likewise, Dr. Saunders' opinion that "patients taking omapatrilat would likely experience 15% to 20% fewer heart-related problems than patients taking enalapril" must be precluded because, again, Defendants failed to give Dr. Saunders the opportunity to consider both sides of the story. (DX 23 ¶ 17.) PX 84, marked as plaintiff's exhibit 1518 at the deposition, is an FDA "Joint Statistical-Clinical Review" that analyzes, inter alia, the OCTAVE trial results. It makes the point, following a lengthy discussion, that the alleged prevention of cardiovascular events with Vanlev "is an argument dependent on the belief that omapatrilat achieved blood pressure reductions that could not have been achieved with more aggressive use of concomitant medications." (PX 84 at FDA 000020.)

Moreover, Dr. Saunders himself, prior to writing his expert report in this matter, was of the belief that the modest mm/Hg reduction advantage exhibited by Vanlev vs. enalapril in OCTAVE can be compensated for by adding a diuretic to therapy with enalapril, which is shown both in PX 489 and his deposition testimony about the meeting evidenced in PX 489:

> Q. I'm going to ask you to turn to the page marked 2 at the top right-hand corner. The second line looks to me to read "is oma better than" --
>
> A. Enalapril, plus diuretics.
>
> Q. Okay. Do you recall having any -- anyone at the meeting asking the question as to whether or not omapatrilat was a better antihypertensive than enalapril plus a diuretic?
>
> A. I definitely recall that.

> Q. And what view did you have in that connection? Did you express a view at that meeting?
>
> A. Yeah. I felt that for blood pressure lowering they were very similar. But I also expressed that there's more -- but you're not completely comparing apples with apples, you're comparing two drugs, enalapril plus diuretic with one drug, omapatrilat, and that is a difference.
>
> But in terms of comparing those two treatments, yes, I would agree with that statement there, that they're similar in terms of blood pressure efficacy.
>
> Q. *Just so that we understand, is it your understanding, or is it your opinion that enalapril plus a diuretic would give comparable blood pressure lowering effect to omapatrilat as monotherapy?*
>
> A. *Yes. The data that was presented would suggest that one could -- could get similar blood pressure lowering by using enalapril with a diuretic, as opposed to using omapatrilat alone.* Now, again, I don't recall all of the data that was submitted to know whether or not that in fact was true of all of the studies, but the point that was raised here, I do recall that being discussed, and that was one of the issues.

(Pl. Ex. 11 34:5-35:20) (emphasis added).

2. Dr. Saunders' Favorable Opinion Concerning Vanlev's Use in African-Americans Is Based on a Limited and Selected Document Set

In his report, Dr. Saunders concludes that "omapatrilat had and has a favorable risk/benefit profile, including in African-American patients. In light of this profile, I would recommend that omapatrilat be approved for the treatment of hypertension, particularly in difficult to treat African-American patients. Were I on the FDA Advisory Committee, I would approve omapatrilat as an effective hypertension treatment." (DX 23 ¶ 9.) However, this opinion was reached without his having seen any of the FDA reviews that were critical of Vanlev's use in African-Americans. (PX 53; 84; 85; 376; DX 73.) Additionally, at his deposition Dr. Saunders was also shown a number of documents discussing the incidence of

angioedema in black women. One of those documents was PX 128, marked as plaintiff's deposition exhibit 265. See Pl. Ex. 11 145:17-20; 148:12-149:11; 151:5-16. When later asked what opinion he had as to whether Vanlev would need a particular warning for black women if approved as a hypertensive medication, Dr. Saunders responded as follows:

> A. Based upon data that you showed me today, which I have to admit I have not seen before, about the black women, what you showed me there, I had not seen that before, but based upon that, I would like to look at it and think about it, and so forth. But it's something I'm seeing for the first time.

(Pl. Ex. 11 255:12-18.)

Defendants' utter failure to provide Dr. Saunders with a balanced, robust set of analyses of Vanlev data render his opinions worthless as a legitimate aid to the fact-finder. Therefore his opinion as to Vanlev's favorable risk-benefit profile, insofar as it relates to African-Americans, must also be precluded.

IV. Defendants Should Be Required to Choose One of Their Four "Cardiology/Hypertension/Clinical Trials" Experts Because Their Proffered Testimony is Cumulative and Repetitive

Defendants designated "Cardiology/Hypertension/Clinical Trials" expert witnesses offer identical and cumulative opinions in the area of cardiology, hypertension and clinical trials. Because such repetitive testimony is a classic example of needlessly cumulative, time-wasting and unfairly prejudicial evidence, Defendants should be required to choose one expert to testify about these matters.

In In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 746 (3d Cir. 1994), the Third Circuit reaffirmed that "under Rule 702, admissibility of scientific testimony turns not only on reliability but also on the possibility that admitting the evidence would overwhelm, confuse, or mislead the jury"; and that Rule 702 partly incorporates Rule 403 analysis with respect to experts. See also Planned Parenthood v. Verniero, 22 F. Supp. 2d 331, 338-43 (D.N.J. 1998)(Hughes, M.J.)

(excluding 10 of defendants' 14 expert witnesses as irrelevant, unnecessary and cumulative pursuant to Fed. R. Evid. 402, 403, 611 and Fed. R. Civ. P. 1 and 16).

> Multiple expert witnesses expressing the same opinions on a subject *is a waste of time and needlessly cumulative.* It also raises the possibility that jurors will resolve competing expert testimony by *"counting heads"* rather than evaluating the quality and credibility of the testimony.

Sunstar, Inc. v. Alberto-Culver Co., No. 01 C 0736, 2004 WL 1899927, at *25 (N.D. Ill. Aug. 23, 2004) (emphases added).

Here:

- All four experts give an overview of hypertension and heart failure. Compare (DX 23 ¶¶ 11-15 (Saunders); DX 27 ¶¶ 9-40 (White); DX 21 ¶¶ 51, 62-63 (Ofili); DX 26 ¶¶ 7-35 (Weir).)

- All four experts discuss Vanlev's risk/benefit profile. Compare (DX 23 ¶ 8, 9, 20-22 (Saunders); DX 27 ¶¶ 78-84 (White); DX 21 ¶¶ 93-103-110 (Ofili); DX 26 ¶¶ 47-52, 60-62, 64-67 (Weir).)

- All four experts discuss Vanlev's risks, namely angioedema. Compare (DX 23 ¶¶ 18-19 (Saunders); DX 27 ¶¶ 48-67, 73-74 (White); DX 21 ¶¶ 67-73, 110-116 (Ofili); DX 26 ¶¶ 47-52 (Weir).)

- All four experts discuss Vanlev's efficacy. Compare (DX 23 ¶¶ 16-17 (Saunders); DX 27 ¶¶ 44-47 (White); DX 21 ¶¶ 93, 103-109 (Ofili); DX 26 ¶¶ 37-38, 59 (Weir).)

- Drs. White, Ofili, and Weir all discuss clinical trial practice and the Vanlev clinical trials, particularly OCTAVE and OVERTURE. Compare (DX 27 ¶¶ 61-66, 68-77 (White); DX 21 ¶¶ 25-92, 94-110 (Ofili); DX 26 ¶¶ 39-46, 53 (Weir).)

Lastly, Drs. White, Ofili and Weir also all discuss the meaning of the phrase "airway compromise" and give assessments of how BMS used the phrase. Their discussions of airway compromise are duplicative of the opinions expressed by Defendants' two "airway compromise" experts, Dr. Murphy and Walls, and should be precluded as discussed in the motion directed at Drs. Murphy and Walls' expert opinion, also submitted herewith.

CONCLUSION

For the reasons set forth above, Lead Plaintiff respectfully requests that the Court grant the instant motion to exclude certain testimony of defendants' four "Cardiovascular/ Hypertension/Clinical Trials" experts, Drs. William White, Elizabeth Ofili, Elijah Saunders and Matthew Weir, together with that of their epidemiology expert Dr. Stephen Kimmel, and to strike that testimony from defendants' summary judgment record.

Dated: May 13, 2005

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